

3.6 Metabolic Diseases

3.6.1 Summary

This section sets out proposals developed by key stakeholders to promote pre-competitive research in Europe that will address the bottlenecks that exist in the development of novel therapies for diabetes. This disease was chosen from the vast variety of metabolic diseases as diabetes is associated with a number of other metabolic abnormalities, such as obesity, dyslipidemia and metabolic syndrome. In addition, the prevalence of diabetes is expanding in an exponential manner from the current 150 million to approximately 250 million in the next 15 years. This disease and its complications cause not only human suffering, but it is also a major economic burden for the society. There is a huge unmet medical need for pharmaceutical therapies for the prevention, treatment and cure of diabetes.

The group has identified five major research priorities:

- Develop more predictable *in vitro*, *in vivo* and *in silico* pre-clinical models for diabetes and its complications;
- Identify and validate novel targets in diabetes by discovery research in the pathophysiology of the disease and its complications;
- Identify and validate biomarkers for beta-cell function and loss, for treating both insulin resistance and diabetic complications;
- Characterise subpopulations and patient groups using genomics and biomarkers for focused therapeutic and preventive studies;
- Develop quality-of-life and patient-reported outcome metrics to measure the impact of novel treatments on daily activities, and the overall benefits of novel therapy.

The objective is to involve all key stakeholders, such as pharmaceutical industry, academic centres, patients, regulators, major associations and European Community in this effort in a collaborative fashion.

3.6.2 Introduction

A multidisciplinary group representing major stakeholders with a broad range of expertise was set up to review the bottlenecks in developing novel therapies for diabetes, and to make proposals for how they should be addressed in a pre-competitive manner. In addition, a number of scientists focusing on diabetes research or drug development were consulted for further opinions and ideas.

The major research areas that need to be addressed concerning the prevention and treatment of diabetes and its complications are glucose metabolism, lipid metabolism, obesity and cardiovascular diseases. As there are other programmes that focus on dyslipidaemia, atherosclerosis and obesity, the focus of this proposal is research for the normalisation of glucose metabolism. Some academic networks already exist in Europe for diabetes projects that were funded by FP5 and 6. There is no specific budget from the European Commission for diabetes research, but 'diabetes' is included in both FP5 and FP6.

FP5

22 projects in most parts of quality-of-life programme as diabetes must be studied from different angles (EU contribution: €42 mn).

FP6 First Call

- DIABESITY (IP) project: € 1.7 mn – Drug targets for obesity/TP2D;
- TONECA (CA): € 1.0 mn – Molecular mechanism of beta-cell death;
- IMMIDIAB (SSA): € 0.2 mn – Type II diabetes in immigrant populations in Europe;
- EUROTHYMAIDE (IP): €12.0 mn – Major biological functions of the thymus, with emphasis on auto-immune cell destruction.

FP6 Second Call

- EXGENESIS (IP): €12.5 mn – Effect of physical activity on human health;
- EUGENE2 (NoE) project: € 8.0 mn – Drug targets for obesity/TP2D;
- BETACELLTHERAPY (IP): €11.8 mn – Beta-cell programming for treatment of diabetes;

- MOLPAGE (IP): €12.0 mn – Bio-markers for early diagnosis and identification of people at risk of diabetes and cardiovascular diseases.

FP6 Third Call

- EuroDia (IP): € 9.2 mn – Functional genomics of pancreatic beta-cells, and of tissues involved in control of the endocrine pancreas for prevention and treatment of TP2 diabetes;
- HEPADIP (IP): €12.0 mn – Hepatic and adipose tissue and functions in the metabolic syn-drome;
- PREDICTIONS (STREP): € 1.8 mn – Identification of biomarkers associated with the risk to de-velop diabetic nephropathy.

FP6 Fourth Call

Two more projects have been submitted to the 4th call; their respective contracts are currently under negotiation:

- SAVEBETA (STREP) – Utilisation of functional genomics to identify pathways responsible for the reduction of beta-cell mass in diabetes;
- INTERACT (IP) – Interaction of genetics and lifestyle on incidence of Type II dia-betes.

3.6.3 Present Status of the Disease Area

Diabetes is an epidemic disease, with 150 million individuals affected around the world; this prevalence is rising exponentially alongside an increase in obesity and a decrease in physical activity. It is estimated that in 10 years' time, the prevalence of diabetes will be 250 million. A majority (90%) of patients have Type II diabetes, characterised by abnormal insulin secretion and insulin resistance. The remaining 10% have Type I diabetes as a consequence of beta-cell loss, and a near total lack of insulin. Recently, there has been an increasing incidence of Type II diabetes, associated with increasing obesity in young age groups. This, again, is probably a result of lifestyle changes. There is also a progressive increase in the prevalence of Type I diabetes in Europe, but the causes for this increase remain unknown.

There is a huge unmet need, and many opportunities to improve diabetes therapy. A majority of diabetic patients on current therapies will develop microvascular complications such as neuropathy, nephropathy and retinopathy. Associated diseases are a life-threatening burden, particularly in Type II diabetes. These include dyslipidaemia, atherosclerosis and other features of metabolic syndrome, leading to problems such as stroke and myocardial infarction. Currently available therapies are not effective enough to normalise glucose and lipid metabolism and thus prevent complications. Although much effort has been made at national level in various European countries to address the problem of diabetes, no significant improvement in glycemic control at the national level has been achieved in Europe or the US during the past couple of decades.

The costs of diabetes are high, both in terms of the human suffering it causes, and the economic burden for the community. In European countries, the diabetes-related direct costs of diagnosis, treatment and care are estimated to be, on average, 5% of total healthcare expenditure. Indirect costs, such as lost productivity resulting from disability or premature death, are about equal to the direct costs.

3.6.4 Bottlenecks

The bottlenecks of drug development for diabetes were prioritised as follows:

- Predictive pharmacology;
- Cell-based and animal models for Type I and Type II diabetes;
- Basic research in the pathophysiology of diabetes and micro- and macrovascular complications;
- Modification of behaviour and lifestyle;
- Identification of biomarkers for beta-cell function, mass and for insulin resistance;
- Validation of the biomarkers *in vivo* and in humans;
- Characterisation of focused patient groups for clinical trials;
- Quality of life.

3.6.4.1 Predictive Pharmacology

3.6.4.1.1 Cell-based and Animal Models for Beta-cell Failure and Insulin Resistance

Scientific approach	<ul style="list-style-type: none"> • Cell based models. Identification of novel markers from high-risk individuals (beta-cell) or markers of insulin resistance in liver, muscle and fat cells (cytokines, adipokines, compounds from NMR analysis and so on), to be introduced and tested in cell models; • Animal models have two steps: first to establish a public database with detailed information on existing models. Second, to develop novel humanised target-specific models such as beta-cell dysfunction and loss, insulin resistance in the liver, muscle or fat cell, micro- or macrovascular vascular complications, and animal models for human islet transplantation.
How it addresses the bottlenecks	Helps to identify novel pathways and targets, improves compound predictability and reduces the attrition rate in drug development. Allows proof of concept to be tested in pre-clinical and early clinical development, reduces the attrition rate throughout the development phase and the scope and cost of clinical trials.
Key players	Academic groups and industry. TONECA network, (www.toneca.com) EURADIA, (www.euradia.org), EURODIA, academic centres, industry.
Infrastructure needs	
Feasibility	Cell-based models are feasible and setting up a common database for existing animal models is easy, but to establish target specific models will be difficult.
Resource allocation	€44 mn.
Metrics of success	Validation with the <i>in vivo</i> models and with human studies.
Generic issues	
Interaction with SRA	Knowledge Management.

3.6.4.1.2 Basic Research in the Pathophysiology of Diabetes and Micro- and Macrovascular Complications

3.6.4.1.2.1 Beta-cell dysfunction and loss

Scientific approach	Molecular signature of functional versus dysfunctional beta-cell using genomics and bioinformatics; this information should be available in open access gene and protein banks. Examine central regulation of beta-cell function, and lipo- and glucotoxicity leading to beta-cell damage. Use available human samples (plasma, tissues) for novel assays, and available data and bioinformatics tools for <i>in silico</i> research to discover predictive biomarkers and factors associated with beta-cell dysfunction and loss, and biomarkers for micro- and macro vascular complications. Establish a European Central facility to co-ordinate isolation and sharing of human islets. Facilitate research to develop beta-cells from adult stem cells.
How it addresses the bottlenecks	Novel therapeutic targets, more focused groups for clinical research, bring genomics to the field, allowing the information from each experimental model to be maximised.
Key players	Beta-cell Gene Exp. Bank (http://tdbase.org/cgi-bin/enter_bcgb.cgi), EURODIA, EURADIA, Eugene2 network (www.eugene2.com), UKPDS

	database, Botnia database, academy, industry, regulatory.
Infrastructure needs	European centre for human islets and a centre for study co-ordination.
Feasibility	Do-able
Resource allocation	€26 mn.
Metrics of success	Novel, druggable targets.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.1.2.2 *Insulin Resistance*

Scientific approach	Examine molecular mechanisms of inflammation, oxidative stress, endoplasmic reticulum stress, endothelial function and their interaction in insulin resistance. Create an open access database of gene expression data in insulin responsive tissues as well as accessible tissues that are regulated by insulin, insulin resistance and diabetes. Use available human samples (plasma, tissues) for novel assays, and available data and novel bioinformatics tools to find out predictors and biomarkers associated with insulin resistance.
How it addresses the bottlenecks	Novel targets.
Key players	UKPDS database, Botnia database, Diabetes genome Anatomy Project, USA (www.diabetesgenome.org/home/index.jsp), Diabetesity, (www.eurodiabetesity.org), Exgenesis, (www.dundee.ac.uk/pressreleases), academy, industry, SMEs, regulators.
Infrastructure needs	Gene databanks, patient databanks.
Feasibility	Do-able, extensive.
Resource allocation	€21 mn.
Metrics of success	Novel targets.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.1.2.3 *Microvascular Complications (retino-, neuro- and nephropathy)*

Scientific approach	Establish target-specific animal models and biomarkers. Examine the contribution of hyperglycemia through different pathways (advanced glycosylated end-products, polyol pathway, protein kinase C, oxidation by free radicals and so on), genetic background and other factors in the pathophysiology of complications. To find associations and causal relationship, use existing human data basis and bioinformatics for <i>in silico</i> research, and blood and tissues samples for novel assays.
How it addresses the bottlenecks	Provides novel targets and biomarkers. Brings the possibility of reducing the size and duration of clinical trials.
Key players	Industry, academy, patient organisations, data bases from large studies (EURODIAB, UKPDS etc), regulators.
Infrastructure needs	Gene databanks, patient databanks, biomarker centre.
Feasibility	Do-able, extensive.

Resource allocation	€14 mn.
Metrics of success	Validated animal model, novel validated targets, successful proof-of-concept studies in focused patient groups.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.1.3 Macrovascular Complications (Atherosclerosis, Stroke)

Scientific approach	Establish target-specific animal models and biomarkers. Use available data and bioinformatics tools as well as novel assays to analyse stored samples from long-term studies to find out associated factors and their potential causal relationship with macrovascular complications. Use novel imaging technologies and biomarkers and personalised medicine (genomics) in prospective studies.
How it addresses the bottlenecks	Provides novel targets and a possibility to reduce the size and duration of clinical studies.
Key players	Industry, academia, databases and stored samples from large studies (UKPDS etc), regulators.
Infrastructure needs	Patient databases, bioinformatics centre, imaging centre.
Feasibility	Do-able
Resource allocation	€14 mn
Metrics of success	Validated animal models and biomarkers. Novel targets. Successful short and small proof-of-concept studies.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.1.4 Modification of Behaviour and Lifestyle

Scientific approach	Develop means to intervene on eating and exercise habits. Find biomarkers and genomic information for responding populations, with the goal of finding personalised and preventive interventions.
How it addresses the bottlenecks	Biomarkers, patient recruitment.
Key players	Patient groups, industry, regulators, academia.
Infrastructure needs	Patient databases, bioinformatics centre.
Feasibility	Difficult.
Resource allocation	€16 mn.
Metrics of success	Validation of biomarkers, successful proof-of-concept studies.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.2 Identification of Biomarkers for Beta-cell Function, Mass and Insulin Resistance

3.6.4.2.1 Beta-cell Function and Mass

Scientific approach	Identify <i>in vitro</i> and <i>in silico</i> markers which detect early changes (preceding hyperglycaemia) in beta-cell mass in pre-clinical models and which predict diabetes progression and deterioration of metabolic control. Use imaging technology with beta-cell-specific probed ligands.
How it addresses the bottlenecks	Reduces the size and duration of <i>in vivo</i> and clinical studies.
Key players	UKPDS, Botnia, Euradia, Eurodia, Eugene2 network, JDRF, academic groups, industry, regulators.
Infrastructure needs	Patient databases, bioinformatics centre, imaging centre.
Feasibility	Do-able, extensive.
Resource allocation	€33 mn.
Metrics of success	Validation in the <i>in vivo</i> models and in clinical studies.
Generic issues	Biomarker centre, imaging centre.
Interaction with SRA	Knowledge management.

3.6.4.2.2 Insulin Resistance

Scientific approach	Identification of factors (<i>in vitro</i> , <i>in silico</i>) to correlate with insulin resistance in whole-body or in specific tissues (muscle, fat, liver), or which can be used as prognostic tools for individuals such as the obese, who are at risk of progressing from insulin resistance to Type II diabetes, and which are reversible with therapy.
How it addresses the bottlenecks	Reduces the size and duration of <i>in vivo</i> and clinical studies.
Key players	As in 2.1.
Infrastructure needs	Patient databases, bioinformatics centre.
Feasibility	Do-able, extensive.
Resource allocation	€27 mn.
Metrics of success	Validation in the <i>in vivo</i> models and clinical studies.
Generic issue	Biomarker centre.
Interaction with SRA	Knowledge management.

3.6.4.2.3 Validation of Biomarkers for Beta-cell function, Mass and Insulin Resistance *in vivo* and in Humans

Scientific approach	<ul style="list-style-type: none"> • Beta-cell. In the first instance, correlate the markers with beta-cell function, mass and morphometry in pre-clinical models. Thereafter, validate the markers in humans with diabetes progression, and with the efficacy of therapeutic approaches; • Insulin resistance. Demonstrate a correlation between the markers and insulin-mediated glucose utilisation in specific tissues (liver, muscle, adipose tissue), and in whole body in pre-clinical models and in humans.
How it addresses the bottlenecks	Validated biomarkers allow reduction in the size and duration of <i>in vivo</i> and clinical studies.
Key players	Industry, academia and regulators.
Infrastructure needs	Patient databases, bioinformatics centre, imaging centre.
Feasibility	Do-able.
Resource allocation	€25 mn.
Metrics of success	Validation.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.3 Characterisation of Focused Patient Groups for Clinical Trials.

Scientific approach	Using genomics and biomarkers to characterise European subpopulations prone to diabetes and, in patient groups, those prone to beta-cell loss, insulin resistance and micro- or macrovascular complications.
How it addresses the bottlenecks	Use of pharmacogenomic markers to predict and select responsive patients will help to reduce the size and duration of clinical trials (personalised clinical investigations). It will also allow preventive trials. This, together with patient registers, would offer a great competitive advantage over low-cost countries.
Key players	Patient organisations, academia, industry, SMEs, regulators.
Infrastructure needs	Patient databases, bioinformatics centre.
Feasibility	Difficult: requires novel technologies, and ethical and political agreements.
Resource allocation	€32 mn.
Metrics of success	Tailored medicine.
Generic issues	Gene banks, biomarker centre.
Interaction with SRA	Knowledge management, Education and Training.

3.6.4.4 Quality of Life

Scientific approach	Develop quality-of-life measures that capture drug efficacy beyond primary efficacy endpoints, and which could also predict the overall health benefits of novel therapies. Develop patient reported outcome tools to quantify therapeutic measures (home blood glucose monitoring) and endpoints (hypos, HbA1c, impact of diabetic complications on daily living and so on).
How it addresses the bottlenecks	Quality-of-life data will help the regulatory approval of novel drugs. Facilitates patient recruitment.
Key players	Industry, regulatory, patient groups.
Infrastructure needs	Patient databases, bioinformatics centre, imaging centre.
Feasibility	Do-able.
Resource allocation	€12 mn.
Metrics of success	Reduced expenses and lost working days.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.5 Resources

The total cost of the recommendations (€264 mn) are estimates for a period of seven years and will be subjects to further analysis as appropriate.

Activities	Costs (€mn)
Develop more predictable pre-clinical models (<i>in vitro</i> , <i>in vivo</i> , <i>in silico</i>) for diabetes and its complications	6.3
Identify and validate novel targets in diabetes by discovery research in the pathophysiology of the disease and its complications	13.0
Identify and validate biomarkers for beta-cell function and loss, for insulin resistance and for diabetic complications	12.1
Characterise subpopulations and patient groups using genomics and biomarkers for focused therapeutic and preventive studies	4.6
Develop quality-of-life and health economic metrics to measure impact of novel treatments on daily activities and the economic benefits of novel therapy	1.7
TOTAL DIABETES (€mn per year)	37.7

3.6.6 List of Contributors

Improved Predictivity of Efficacy Evaluation: Metabolic Diseases (Diabetes)			
Stakeholders Group	Last Name	First Name	Institution
European Commission	Nimmesgern	Elmar	DG Research
Academia	Eizirik	Decio L.	Brussels Free University
	Ferrannini	Ele	University of Pisa
	Gale	Edwin	University of Bristol
	Groop	Leif	University of Lund
	Halban	Philippe	University of Geneva
	Lenzen	Sigurd	Hannover Medical School
	Taskinen	Marja Ritta	University of Helsinki
	Wollheim	Claes	University of Geneva
Regulatory Authorities	Stötter	Hans	Swiss Medic
Companies, Pharma & SME	Dejgaard	Andres	NovoNordisk
	Gromada	Jesper	Eli Lilly
	Koivisto (Chair)	Veikko	Eli Lilly
	Mest	Hans-Jürgen	Eli Lilly
	Porksen	Nils	Eli Lilly
	Ragan	Ian	Eli Lilly
	Seedorf	Klaus	Eli Lilly
Patient Organisations	Henrichs	Helmut	International Diabetes Federation
Others	Brendel	Carole	EURADIA